throughout the specification, for example at page 17, line 12. Claim 11 is amended to correct form. Claim 19 has been withdrawn from consideration.

No new matter is added. Reconsideration of the application is respectfully requested.

Telephone Conference

Applicant thanks Examiner Gary Kunz for the helpful telephone conferences with the Applicant's representative on October 23, 2002, wherein the claims were discussed. The Applicant appreciates the time and effort of Examiner Kunz in reviewing the prior art of record and discussing claim amendments.

The Applicant's other applications and issued patent were discussed with Examiner Kunz. The Applicant's co-pending applications were listed on the Information Disclosure statement submitted on July 14, 1999; U.S. Patent Application No. 09/288,061 (listed on this Information Disclosure Statement) has now issued as U.S. Patent No. 6,210,974.

Claim Objections

Claim 11 was objected to as being in improper form, and for including a typographical error. Claim 11 has been amended to include the selection step of assaying for rotamase activity, as suggested in the Office action, and to correct the typographical error, thereby removing the objection.

Rejections Under 35 U.S.C. 112, first paragraph

Claims 20 and 21 are rejected as allegedly there is insufficient written description for the claimed methods. Claim 21 is canceled. Applicant respectfully disagrees with the rejection.

The Office action alleges that because a sufficient number of FK506 analogs are not described, a method for screening FK506 analogs cannot be enabled. However, the claims are directed to *assays*, not to the compounds themselves. As stated in 35 U.S.C. §112:

> the specification shall contain a written description of the invention, and the manner and process of making and using it....the specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

In the present application, the claims are directed to a *method,* specifically a method for identifying an FK506 analog that stimulates nerve cell growth. The specification provides adequate written description for this method. Specifically, exemplary FK506 analogs to be screened using the method are described on page 6, line 12 to page 19, line 3. Applicant notes that one of skill in the art can readily identify an FK506 analog and thus could readily determine other compounds that could be screened using the methods disclosed herein.

The specification need not include an exhaustive exemplification of all of the compounds within a class of known compounds (e.g. FK506 analogs) in order to support a claim which includes reference to the known class (*In re Kamal et al.*, 398 F.2d, 158 USPQ 320 (CCPA 1968); *Ex parte Maxey et al.*, 177 USPQ 468 (POBA 1972)). As pointed out in a decision involving chemical claims, "appellants [here, applicant] are **not** required to disclose every species encompassed by their claims even in an unpredictable art" (emphasis in original). *In re Angstadt*, 537 F.2d 498,503 (CCPA 1976). Such a holding is reasonable, since it is very difficult if not impossible to test and disclose all operative species. Further, to require so would apparently necessitate a patent application with an enormous number of working examples. As the *Angstadt* court explains:

> Such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid "literal" infringement of such claims by merely finding another analogous catalyst complex could be used in forming hydroperoxides.

Thus, in the present application a potential infringer could readily avoid "literal" infringement of such claims by merely finding another nerve growth promoting agent, other than a specified FK506 analog.

In other words, all the law requires is that a patent applicant prove a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the claims. As a corollary of the *Angstadt* holding, neither is it necessary to list all possible analogs in the claims as long as one skilled in the art would know how to select operable analogs. *Atlas Powder Co. v. E.I. duPont de Nemours & Co.*, 224 U.S.P.Q. 409, 413-14 (CAFC 1984). This is clearly provided in the present specification. Methods for identifying FK506 analog with a specific K_d

for FKBP-12 are described on page 17, lines 9-17. Several exemplary assays for nerve cell growth are described in the specification on page 23, line 10 to page 26, line 1, and in the examples (e.g., page 27, line 6 to page 31, line 28).

However, even if one were to take the view that in order to provide written description for an assay, that the FK506 analogs themselves must be identified, Applicant submits *that the specification clearly provides an adequate amount of information.* Specifically, FK506 analogs are described in the specification on page 6, line 12 to page 19, line 3. Chemical structures and molecular weights are provided, as are descriptions of derivatives, and references to publications and patent documents that are readily available to one of skill in the art. Moreover, methods for determining FKBP-12 binding are described, and appropriate references are provided (for example, see page 17, lines 9-17).

Furthermore, both *in vivo* and *in vitro* assays of neurite outgrowth with several FK506 analogs are presented in the specification. Indeed the specification discloses that V-12,559, a FK506 analog which does not bind FKBP-12, produces larger axonal calibers and more myelinated fibers (see Example 2 of the specification at page 31, line 16-28). Thus a known FK506 analog, which does not bind FKBP-12, is shown to stimulate neurite outgrowth. Thus, Applicant submits that the specification clearly provides adequate written description for the claimed methods.

Rejections Under 35 U.S.C. § 112, second paragraph

Claims 6-7, 9-11, 15-17 and 20-21 were rejected as allegedly indefinite in reciting that an FK506 analog does not bind FKBP-12, and then specifying a K_d of binding. Claims 9-10, 16-17 and 21are canceled. Applicants respectfully disagree with this assertion as applied to claims 6-8, 11, 15 and 20. However, solely to advance prosecution, the claims have been amended to remove the term "non-binding," thereby removing the rejection.

Rejections Under 35 U.S.C. § 102

Claims 6-7, 9, 11 and 15-16 are rejected under 35 U.S.C. § 102 as being anticipated by U.S. Patent No. 5,801,197 (the '197 patent). Claims 9, 16-17 and 21 are canceled. Applicant respectfully disagrees with this rejection as applied to amended claims 6-7, 11 and 15.

Claim 6 has been amended to recited that the FK506 analog has an apparent K_d for FKBP-12 of greater than 100 μM. Thus, claim 6 has been amended to incorporate the limitations of claim 10.

The '197 patent discloses that FK506 analogs that *have* an affinity for FKBP-12 also inhibit rotamase (see column 1, first paragraph, line 2, column 2, lines 60-61, and column 4, lines 13-15). In fact, the description of the invention states (column 4, lines 10-15): "The novel neurotropic FKBP inhibitor compounds of this invention have an affinity for the FK506 binding proteins such as FKBP-12" and (column 7, lines 7-9) "[t]he very close correlation between the potencies of drugs in binding to immunophilins, inhibiting their rotamase activity and stimulating neurite outgrowth..." Thus, the '197 patent teaches selection of FK506 analogs with a high affinity for FKBP-12, and *teaches away* from selection of an FK506 analog that *does not bind* FKBP-12, as specified in the pending claims. Furthermore the '197 patent teaches selection of FK506 analogs that inhibit rotamase, and *teaches away* from selecting a compound that does not inhibit rotamase activity as specified in the pending claims (e.g., claim 11).

Applicant notes that Table 1 of the '197 patent describes a K_i test procedure; the data presented in Table 1 show a K_i of rotamase inhibition. Thus compound 7 shown in Table 1 has a K_i for rotamase activity of 80 μM. The '092 patent does not suggest, nor render obvious selecting a FK506 analog that has an apparent K_d for FKBP-12 of greater than 100 μM, as recited in claim 6.

Thus, the '197 patent does not suggest, nor render obvious, the subject matter of amended claims 6-7, 11 and 15. Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 6-7, 9, 11 and 15-16 were rejected as allegedly being anticipated by U.S. patent No. 5,717,092 (the '092 patent). Claims 9, 16-17 and 21 are canceled. Applicant respectfully disagrees with this rejection as applied to amended claims 6-7, 11 and 15.

The '092 patent teaches that "The neurotrophic activity of the compounds of this invention is directly related to their affinity for FKBP12 and their ability to inhibit FKBP12

rotamase activity" (see column 15, lines 49-51). Thus, the '092 patent teaches a direct correlation between a high binding affinity for FKBP-12 and an effect on neurite outgrowth; the '091 patent teaches away from compounds with a high K_d for FKBP-12. Table 2 of the '092 patent (column 44) shows the cytotoxic activity of FK506 analogs. Example 9 describes that various concentrations of an FKBP-12 binding compound (0.1 to 10 μM amounts) were added to FKBP-12, and rotamase activity was measured (not Kd). The values shown in the Table in column 45 are K_i of rotamase inhibition. The examples states that preferred FKBP12 binding agents have high rotamase inhibition. Only compounds that bind FKBP with a high affinity, and inhibit rotamase, are tested for their ability to stimulate neurite outgrowth (see column 45, lines 40-41). Thus, the '092 patent does not suggest, nor render obvious selecting a FK506 analog that does not inhibit rotamase activity, as recited in claim 11. Moreover, the '092 patent does not suggest, nor render obvious selecting a FK506 analog that has an apparent K_d for FKBP-12 of greater than 100 μM, as recited in claim 6.

Thus, the '092 patent does not suggest, nor render obvious, the subject matter of amended claims 6-7, 11 and 15. Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 6-7, 9, 11 and 15-16 were rejected as allegedly being anticipated by Steiner et al. (*Nature Medicine* 3:421-8, 1997).

Steiner et al. teaches evaluation of FK506 analogs for FKBP-12 binding activity. However, Steiner et al. teaches that compounds that bind FKBP-12 with a high affinity promote neurite outgrowth, and suggest selecting FK506 analogs based on this activity. Steiner et al. also suggests that potency in stimulating nerurite outgrowth is the same as the potency in inhibiting rotamase activity. Thus, Steiner et al. teaches the selection of compounds that inhibit rotamase activity. Steiner et al. does not suggest selecting FK506 analogs that do not bind FK506. By teaching that the characteristic of FKBP-12 binding is desirable, and that inhibition of rotamase activity is desirable, Steiner et al. *teaches away* from the claimed methods (which include selecting an FK506 analog that binds FKBP12 with a Kd of 100 μM, and selecting compounds that do not inhibit rotamase activity).

The Office action states that Steiner et al. is silent as to the K_ds of the disclosed compound. The Office action further contends that as the relationship of FKBP-12 binding with neurite outgrowth is disclosed, that the reference must inherently teach the claimed methods.

Applicant respectfully disagrees. One cannot ignore the broader, instructive disclosure of a reference (*In re Cortright*, 377 F2d 647, 153 (CCPA 1967)). As disclosed above, Steiner et al. teaches the selection of compounds with a high affinity promote neurite outgrowth, and teaches the selection of compounds that inhibit rotamase, and thus *teaches away* from the claimed methods. Moreover, claim 6 has now been amended to recite selecting a FK506 analog that has an apparent K_d for FKBP-12 of greater than 100 μM. Clearly, Steiner et al. does not disclose selecting a FK506 analog with this particular property.

Thus, Steiner et al. does not suggest, nor render obvious, the subject matter of amended claims 6-7, 11 and 15. Reconsideration and withdrawal of the rejection is respectfully requested.

Rejections Under 35 U.S.C. § 103

Claims 10 and 17 were rejected as allegedly being obvious over the '197 patent, the '092 patent, and Steiner et al., alone or in combination. Claims 10 and 17 have been canceled. Applicant respectfully disagrees with this rejection as it might be applied to claim 6 as amended.

The rejections appear to be based on assumptions regarding properties allegedly inherent in the experiments described in the prior art. With novelty, a single prior art reference may anticipate because of what it inherently discloses (*Typer Refrigeration Corp. v. Kysor Industrial Corp.*, 777 F.2d 687, 227 USPQ 845 (Fed. Cir. 1985)). Such an inherent feature may be relied upon only if it such inherency would be obvious to one of skill in the art *(Kloster Speedsteel AB v. Crucilbe Inc.* 793 F.2d 1565, 1576; 230 USPQ 88,88 (Fed. Cir. 1986)). The '197 patent, the '092 patent, and Steiner et al. teaches that compounds with a high affinity for FKBP-12 promote neurite outgrowth. Thus, it *teaches away* from selecting a compound with a low affinity. It is difficult to fathom how a selecting a FK506 analog with a specific K_d, let alone a K_d of 100 μM, is suggested by any of these references, either alone or in combination.

Thus, it would not be inherently obvious for one of skill in the art to select an FK506 analog with a K_d of greater than 100 μM based on the teaching of the '197 patent, the '092 patent, or Steiner et al. Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

If any minor matters remain to be addressed, the Examiner is respectfully requested to call the undersigned patent agent at the telephone number listed below.

Respectfully submitted,

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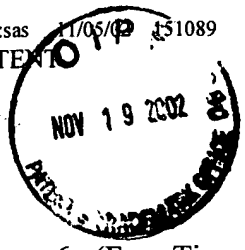

Marked-up Version of Amended Claims
Pursuant to 37 C.F.R. §§ 1.121(b)-(c)

6. (Four Times Amended) A method of identifying a [non-binding] FK506 analog that stimulates nerve cell growth, the method comprising:

screening a plurality of FK506 analogs for binding to FKBP-12;

selecting a FK506 analog [that does not bind FKBP-12 wherein the compound that does not bind FKBP-12 is a compound] that has an apparent K_d for FKBP-12 of greater than [10] 100 μM; and

assaying the FK506 analog [that does not bind FKBP-12] for activity in promoting nerve cell growth, thereby identifying a [non-binding] FK506 analog that stimulates nerve cell growth.

7. (Reiterated) The method of claim 6, wherein the method does not comprise selecting an agent based on its ability to inhibit FKBP-12 rotamase activity.

Please cancel claims 9 and 10, without prejudice to renewal.

11. (Twice Amended) The method of claim 6, [wherein the FK506 analog does not inhibit FKBP-12 rotomase activity] further comprising selecting a FK506 analog that does not inhibit rotamase activity.

15. (Twice Amended) The method of claim 6, wherein the assay for activity in promoting nerve cell growth comprises exposing a cell to the selected [non-binding] FK506 analog and determining if neurite outgrowth is promoted.

Please cancel claims 16-17, without prejudice to renewal.

19. (Withdrawn from Consideration) The method of claim 18, wherein selecting one or more FK506 analogs comprises selecting one or more analogs that do not substantially inhibit FKBP-12 rotamase activity when administered to a pateint at dosage levels up to about 100 mg/kg body weight/day.

20. (Twice Amended) A method of identifying a FK506 analog that stimulates nerve cell growth, the method comprising:

screening a plurality of FK506 analogs, [selected from group consisting of the analogs of claim 21], for binding to FKBP-12;

selecting one or more FK506 analogs of interest that [does not bind FKBP-12, wherein the FK506 analog] has a K_d for FKBP-12 of at least [10] 100 μM; and

assaying of one or more of the analogs of interest for activity in promoting nerve cell growth.

Please cancel claim 21, without prejudice to renewal.